

(2) Different fractions obtained during the course of analysis from the bark including the petroleum ether, alcoholic and aqueous extracts and colouring matter were found not to show any marked physiological activity.

(3) An alcoholic extract prepared from the bark was tried in a number of patients suffering from cardiac decompensation but it did not show any appreciable effects such as are produced with the cardiac tonic drugs of the British Pharmacopœia.

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## A PRELIMINARY NOTE ON THE ACTION OF VASOPRESSIN AND OXYTOCIN.\*

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THE physiological properties of extracts of the posterior lobe of the pituitary body are well known. Briefly, they cause marked vaso-constriction and raise the blood pressure; they stimulate uterine contractions and are also diuretics. As opposed to this last observation, they markedly reduce the secretion of urine in the disease called diabetes insipidus. But chemical information regarding the physiologically active constituents of pituitary extracts is very meagre. Much controversy has raged round the question, whether these various physiological activities are due to one hormone or to more than one active principle. The general conclusion that can be drawn, from the work that has been done, is that the physiological activity of extracts of the posterior lobe of the pituitary body is due chiefly to two active principles, one tending to cause a rise of blood pressure and the other having a specific oxytocic action. According to Schafer, the principle which acts upon intestinal muscle differs from the above two and there is little doubt that it is histamine. It is probably histamine that is also responsible for the primary fall of blood pressure observed in some samples. Such samples of the extract as do not exhibit this phenomenon have little action on the intestinal muscle.

Recently O. Kamm and his associates (1928) working in the research laboratory of Parke Davis & Co. have succeeded not only in demonstrating the presence of the two important active principles but they have also been able to separate these two and concentrate them in the form of potent solid preparations. They have shown that solutions of these separated active principles can be recombined to form a pituitary extract identical with the original from

which they were prepared, thus proving that no decomposition has taken place. Both active principles are said to be basic bodies, presumably amines; practical manufacturing methods have been developed for the separation of these two hormones and these have been made available for experimental and clinical study. The oxytocic principle named *a-hypophamine* is put up in ampoules and designated *oxytocin*. The pressor principle or *b-hypophamine* has been labelled *vasopressin*. There is at present only one official standard for extracts of the posterior lobe of the pituitary gland and this is based upon the oxytocic test as described in the U. S. P. The amount of activity contained in 1 c.cm. of the official extract has been designated "10 international units." When extracts are prepared from a good grade of gland there is a fairly constant relation between the amount of oxytocic and pressor activities. So the original workers have designated the amount of pressor activity in 1 c.cm. of the official extract as "10 pressor units." Ordinary pituitrin as marketed for obstetrical purposes, therefore, contains 10 oxytocic units and 10 pressor units per c.cm. Pituitrin as marketed for surgical purposes contains 20 oxytocic units and 20 pressor units. The oxytocin put up for experimental work is said to assay 10 oxytocic activity per c.cm. but its pressor activity is only  $\frac{1}{2}$  a unit per c.cm. It is claimed that vasopressin contains 20 pressor units per c.cm. Its oxytocic activity is less than one unit per c.cm. From the results shown above, these authors claim that the purified active principles are bound to have a wider range of clinical use.

These active principles have been subjected to a more complete physiological study by J. H. Gaddum (1928). According to him, oxytocin has, in addition to its action on the uterus, a depressor (blood pressure) action on the fowl and, in certain circumstances, on the cat. Vasopressin, in addition to its effects on the blood pressure and on the kidney (diuresis), has a specific stimulant action on the bowel of the rabbit and a dilator action on the melanophores of the frog; the latter effect is apparently due to a different principle, so that vasopressin is not yet a physiologically pure preparation. A. W. Bourne and J. H. Burn (1928) examined the action of the separated constituents of pituitary extract on the human uterus in labour. They found that oxytocin possesses the typical stimulant action whereas vasopressin has no effect even in large doses. A given dose of oxytocin (2 units) was found to produce a large response in one patient and a small one in another. Discussing the rare cases of pituitary shock which have led to a disinclination on the part of some obstetricians to use pituitary extract, they recommend that oxytocin, having none of the vasomotor effects which are responsible for the collapse, may be confidently used. F. R. Curtis and J. W. Pickering (1928) studied the effect of these active principles on the blood. According to them, vasopressin increases the coagulability of blood both in fasting

\* Messrs. Parke Davis & Co., have now changed these names to Petressin and Pitocin respectively.



animals and in those at the height of digestion. After severe hæmorrhage, vasopressin either has no augmentary effect or delays the coagulability of blood. Oxytocin, when intravenously injected into cats increases the clotting time of blood. The injection of oxytocin after hæmorrhage produces increased coagulability. The failure of vasopressin to increase coagulability of blood after hæmorrhage decreases its hæmostatic value. The ability of oxytocin to convert hypo-coagulability into hyper-coagulability after hæmorrhage should be of considerable advantage during and after labour, when the contractile action of oxytocin on the uterus is supplemented by more rapid clotting of the blood with hardly any increase of blood pressure.

We have, at the outset, to thank Messrs. Parke Davis & Co. for supplying us with two boxes of vasopressin and oxytocin for experimental work. It was our desire to examine and see if we could substantiate the claims made for these two active principles. But as the supply was very

with a standard brand of pituitrin available on the market. As in our previous experiments we had invariably obtained better results with P. D. & Co.'s pituitrin, we used a potent sample of this as standard for comparison. Our experiments were done on cats and guinea-pigs. In order to observe the action of these substances in the intact animals, we used pithed cats, in which the medulla was completely destroyed by passing a convenient sharp instrument through the foramen magnum.

The blood pressure tracings were recorded as usual and the uterine graphs were obtained by Barbour's method as modified by Chopra and David (1927). Injections were given at intervals of one hour allowing sufficient time for the effects of the previous injection to pass away. The action on the isolated guinea-pig's uterus was studied by means of Dale's uterine bath.

Fig. 1 shows the effect of intravenous injections of the active principles on the blood pressure and uterine movements of a pithed cat.

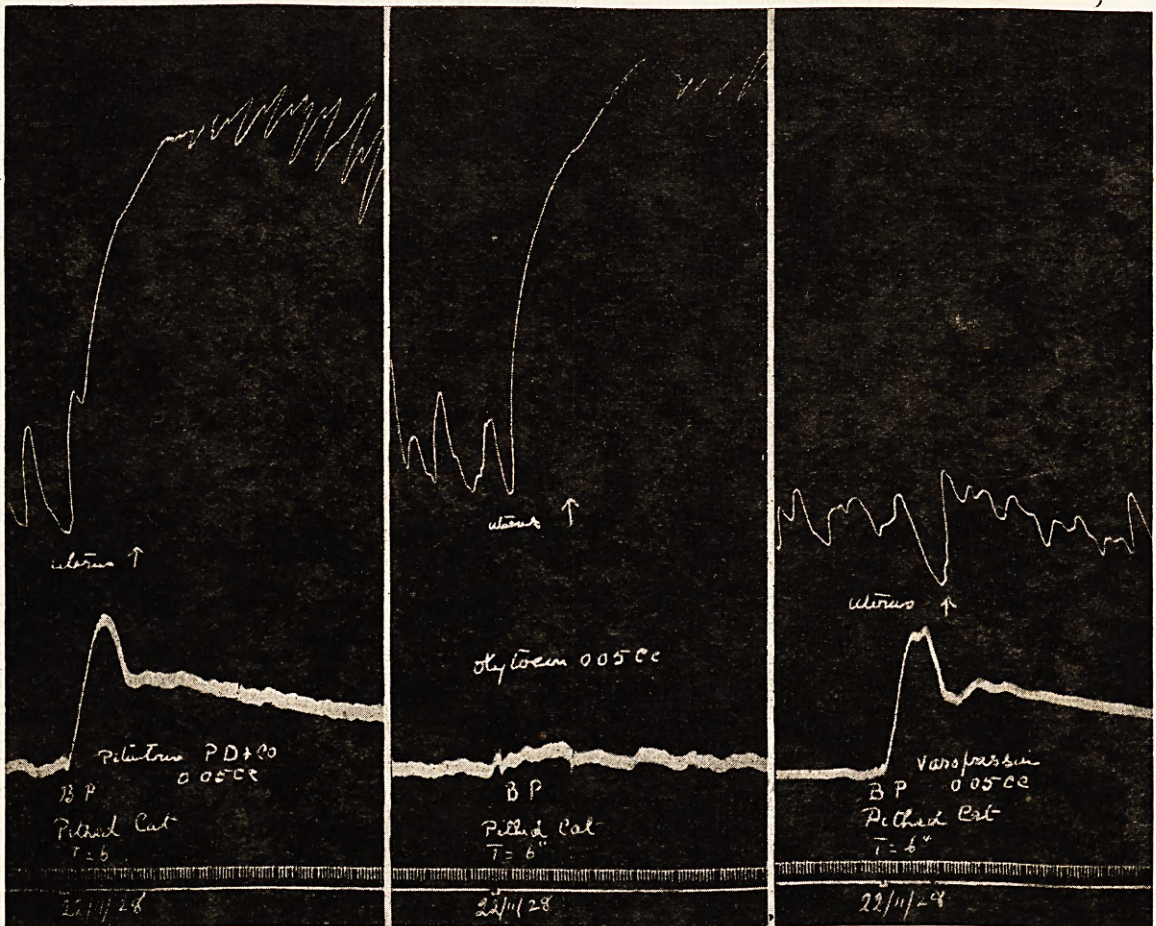


Fig. 1.

(a)

(b)

(c)

limited our observations also had necessarily to be restricted.

Our method was to assay these two substances and compare their oxytocic and pressor values

0.05 c.cm. doses of pituitrin and vasopressin produce the same rise of blood pressure. 0.05 c.cm. of oxytocin and the same dose of pituitrin cause the same height of uterine contraction. With



vasopressin, generally only a slight contraction of the uterus is noticed or there may be no effect at all. But when the uterus is unusually irritable as in pregnancy, an appreciable contraction has been noticed. The character of the contraction is not identical with what is obtained either with pituitrin or oxytocin. While with the latter there is an immediate and steadily increasing tonic contraction, in the case of vasopressin the organ relaxes between contractions exhibiting a "staircase phenomenon." After the full height of contraction is reached the uterus relaxes quickly even before the bath is washed out.

Fig. 2 shows the effect on the isolated non-pregnant uterus of the guinea-pig: 1 in 3000 dilutions (0.05 c.cm. in 150 c.cm.) of oxytocin and

pituitrin generally produce the same height of contraction, while an identical dose of vasopressin either produces no effect at all or only a slight contraction or just an increase of the automatic movements.

0.25 c.cm. vasopressin, i.e., a dilution of 1 in 600 in the bath, exhibits about the same oxytocic activity as 0.01 c.cm. of pituitrin, i.e., 1 in 15,000 dilution. This indicates that the oxytocic activity of vasopressin is about 4 per cent. of that of pituitrin (Fig. 3 a and b).

Intravenous injection into a pithed cat of 0.5 cc. of oxytocin causes about the same rise of blood pressure as 0.025 c.cm. of pituitrin; showing that oxytocin has about 5 per cent. pressor activity as compared with pituitrin (Fig. 3 c and d).

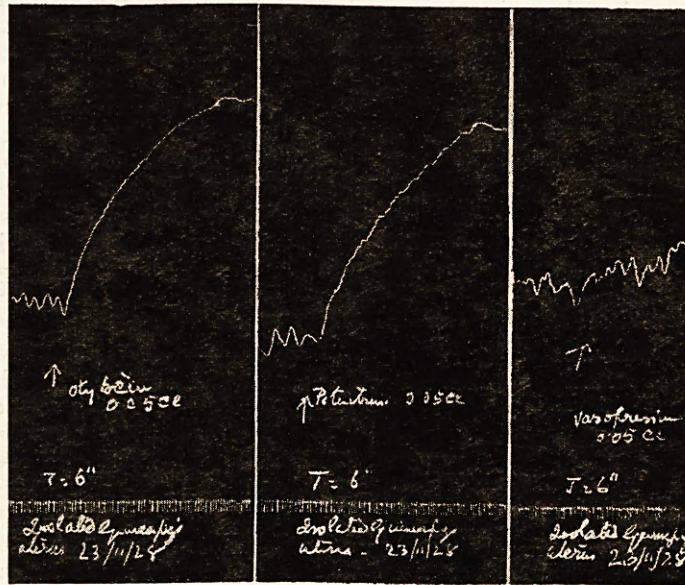


Fig. 2.

(a)

(b)

(c)

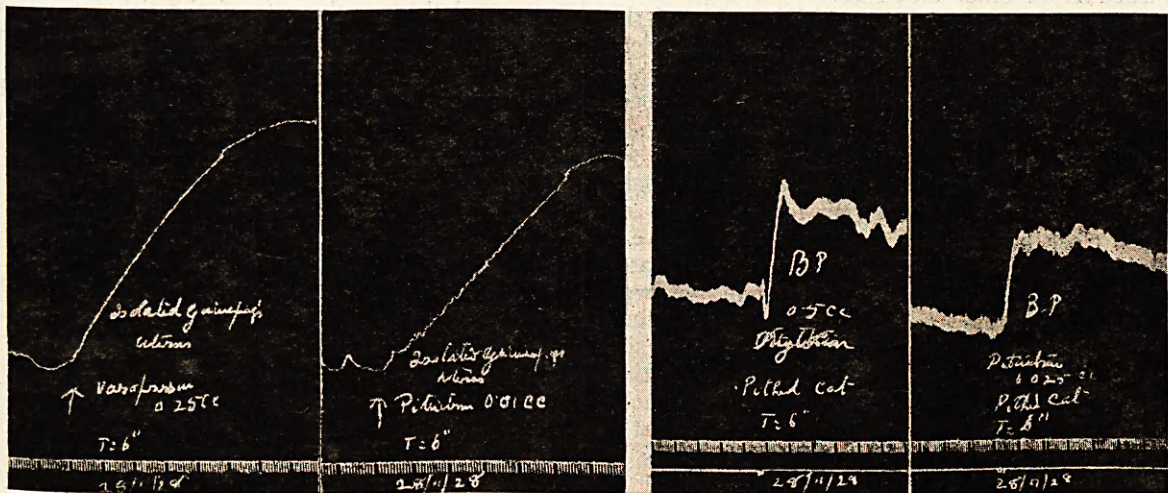


Fig. 3.

(a)

(b)

(c)

(d)



### Summary and Conclusion.

(1) The action on the blood pressure and uterine contractions of the separated active principles of the posterior lobe of the pituitary gland, designated *vasopressin* and *oxytocin* been studied.

(2) While the pressor activity of vasopressin equals that contained in the same quantity of pituitrin, its oxytocic value is only about 4 per cent.

(3) The oxytocic action of oxytocin is about the same as that of pituitrin; but its pressor activity assays only about 5 per cent.

(4) The results obtained by us, as well as by previous workers, indicate that oxytocin is a valuable substitute for the whole extract in obstetric cases especially where a rise of blood pressure is undesirable, as in eclampsia.

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## THE HISTORY OF TICK-BITES IN CASES OF TICK-TYPHUS IN INDIA.

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CASES of tick-typhus are sporadic in occurrence in India and are usually found distributed in hilly tracts with forests or jungle close by. The localities in which cases of typical tick-typhus have occurred are:—Sat Tal (Kumaon), Narayangunj (Dacca), Balaghat (C. P.), Bangalore (Mysore), Malakand (N. W. Frontier) and Kalimpong (Darjeeling).

The characteristics of tick-typhus as distinguished from other allied fevers have been discussed by Megaw and Rao (1928). Out of the cases discussed in that paper, eight cases of tick-typhus gave a definite history of tick-bite, while in nearly all the other cases the circumstances were such that there was a great probability of a tick-bite which was apparently not noticed by the victim. In several instances the attacks started some days after a visit to the forests or jungle close by, or under circumstances where a tick-bite was very likely. A few of the cases totally denied any history of a tick-bite, but even in such cases, one cannot be too sure that they were not bitten by ticks. Tick-bite is easily overlooked, because of the perfectly unirritating and painless manner in which the tick attacks man. That ticks can stay on man without the victim noticing them for prolonged periods is quite possible. Two instances are described in this article where the presence of attached ticks on the person of two naturalists was not observed by them for long periods. As this has

happened to people with full knowledge of the habits of ticks, and who took particular precautions to avoid tick-bites, it is easily understood how likely it is that tick-bites are overlooked by lay persons.

Mr. S., a geologist, went to Assam in connection with his professional work, in December 1923, and had occasion to go into the forests in the district of Sylhet. He stayed there for a few days, and then returned to Calcutta. Seventeen days after his return to Calcutta, he reported the presence of a tick on his person on the left side of the lower abdomen. I found the tick almost completely imbedded in the skin, and only the posterior portion was seen from outside. The skin around the tick-bite had become swollen and indurated and had almost hidden the tick from view. The tick was extracted and in the region of the bite was a very large induration over an inch in diameter. No identification of the specimen was made as it was unfortunately lost.

The point of interest in this case is that this geologist, who knows what a tick is like, was not aware of the presence of the tick on his body for a period of over seventeen days, although he had a bath with soap and hot water every day.

Mr. I., an entomologist, in 1928 went into the Sukna forests in the Darjeeling Terai to collect insects. After every visit into the forests, he took care to collect all ticks on his clothing and body, and had a bath with plenty of soap, a procedure followed by the local people to get rid of ticks; Mr. I. took every care to get rid of ticks on his person, and, being an entomologist himself, knew how to do it.

Eight days after he returned to Calcutta, he felt a scab sticking to his body on the left side of the lower abdomen. On examination it was found to be a tick, which had half buried itself in the body. There was no pain at the site of the bite, and there was a hard induration, half an inch in diameter. After very hard pulling at the tick, only the body of the tick came off, the mouth-parts being left inside. The writer subsequently extracted the mouth-parts of the tick by cutting into the tissues with a Hagedorn needle and after a good deal of dissection. Even then it was found that the apical half of the right mandibular sheath and right mandible were broken and left within the tissue. The photo-micrograph reproduced here (Fig. 1) is of the mouth-parts extracted from the body of the victim. The tick has been identified as the nymphal stage of *Rhipicephalus hamaphysaloides* Supino.

Two points of interest arise out of the present instances.

Sufferers from typical tick-typhus have frequently asserted that they have had no history of tick-bite. Such cases are easily understood in view of the present instance. Here a specialist in entomology had not observed the presence of a tick on his body for a period of over eight days, although he had made a search for them on his person and had a bath every day. When under such conditions the tick had escaped notice,